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Original Paper

Early Blood Pressure Lowering Does Not Reduce Growth of Intraventricular Hemorrhage following Acute Intracerebral Hemorrhage: Results of the INTERACT Studies

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Key Words

Stroke · Intracerebral hemorrhage · Intraventricular hemorrhage · Hypertension · Intensive blood pressure lowering

Abstract

Background: Intraventricular hemorrhage (IVH) extension is common following acute intracerebral hemorrhage (ICH) and is associated with poor prognosis. **Aim:** To determine whether intensive blood pressure (BP)-lowering therapy reduces IVH growth. **Methods:** Pooled analyses of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT1 and INTERACT2) computed tomography (CT) substudies; multicenter, open, controlled, randomized trials of patients with acute spontaneous ICH and elevated systolic BP, randomly assigned to intensive (<140 mm Hg) or guideline-based (<180 mm Hg) BP management. Participants had blinded central analyses of baseline and 24-hour CT. Association of BP lowering to IVH growth was assessed in analysis of covariance. **Results:** There was no signif-

Clinical trial registration: <http://www.clinicaltrials.gov> (unique identifier: NCT00716079).

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icant difference in adjusted mean IVH growth following intensive (n = 228) compared to guideline-recommended (n = 228) BP treatment (1.6 versus 2.2 ml, respectively; p = 0.56). Adjusted mean IVH growth was nonsignificantly greater in patients with a mean achieved systolic BP ≥ 160 mm Hg over 24 h (3.94 ml; p trend = 0.26). **Conclusions:** Early intensive BP-lowering treatment had no clear effect on IVH in acute ICH.

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Introduction

Approximately one third of patients with acute spontaneous intracerebral hemorrhage (ICH) have intraventricular hemorrhage (IVH) extension, which confers a worse prognosis [1]. High blood pressure (BP) is associated with both hematoma growth and poor outcome [2], but limited data exist on the relationship of BP and IVH [3]. We aimed to determine whether BP-lowering therapy is associated with IVH growth among participants of the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials (INTERACT1 and INTERACT2) [2, 4].

Methods

The INTERACT studies were international, multicenter, prospective, open, blinded-endpoint, randomized controlled trials, described in detail elsewhere [2, 4]. They involved 3,243 ICH patients (<6 h of onset; 404 INTERACT1, 2,839 INTERACT2) and elevated systolic BP (150–220 mm Hg) randomly assigned to intensive (target systolic BP <140 mm Hg) or guideline-recommended (<180 mm Hg) BP management. In predefined computed tomography (CT) substudies, 1,310 consecutive patients (346 INTERACT1, 964 INTERACT2) had a second CT at 24 ± 3 h. ICH and IVH volume analyses were performed centrally by expert assessors blind to other data using MISTar version 3.2 (Apollo Medical Imaging Technology). The ethics committees approved the study protocols and written informed consent was obtained from the patients or appropriate surrogates.

Absolute increase in IVH volume was log-transformed to remove skewness and to achieve near-normal distribution of data for analyses. The association of randomized BP-lowering treatment on the absolute increase in IVH volume over 24 h was assessed in analysis of covariance (ANCOVA), adjusted for age, sex, baseline IVH volume, ICH location and volume, and China region. The mean achieved systolic BP over 24 h was calculated from the average of 1, 6, 12, 18, and 24 h postrandomization readings; their association with absolute increase in IVH volume was assessed by ANCOVA adjusting for the same variables, and also for use of statin therapy, baseline systolic BP, and randomized treatment. A p value <0.05 was considered statistically significant and SAS version 9.3 (SAS Institute, Cary, N.C., USA) was used in all analyses.

Results

There were 456 CT substudy participants with IVH and available data (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000448897). Guideline-treated patients were more likely to be female, but otherwise there were no significant differences in baseline characteristics, including time from onset to randomization, BP, as well as ICH and IVH volumes (table 1).

Table 1. Characteristics of patients by randomized treatment

Characteristic	Intensive group (n = 228)	Guideline group (n = 228)	p value
Demographics			
Age, years	67 (13)	68 (12)	0.28
Female	75 (33%)	97 (43%)	0.03
Chinese region	113 (50%)	112 (49%)	0.93
Medical history			
Previous IVH	15 (7%)	17 (8%)	0.72
Previous ischemic stroke	23 (10%)	28 (12%)	0.47
Heart disease	10 (4%)	9 (4%)	0.81
Hypertension	161 (71%)	168 (74%)	0.51
Diabetes mellitus	32 (14%)	27 (12%)	0.47
Medication history			
Antihypertensive agent	119 (52%)	118 (52%)	0.89
Oral anticoagulant	18 (8%)	14 (6%)	0.46
Antiplatelet therapy	38 (17%)	40 (18%)	0.80
Lipid-lowering therapy	27 (12%)	26 (11%)	0.87
Clinical features			
Time from onset to randomization	3.7 (2.7–4.7)	3.5 (2.8–4.7)	0.89
Systolic BP	181 (17)	181 (17)	0.81
Diastolic BP	99 (15)	100 (15)	0.37
Glasgow Coma Scale score ¹	14 (12–15)	14 (12–15)	0.35
NIHSS score ²	14 (9–18)	14 (9–19)	0.51
NIHSS score ≥15	102 (45%)	113 (50%)	0.28
CT findings			
Time from onset to first CT, h	1.8 (1.3–2.6)	1.8 (1.2–2.5)	0.61
Baseline hematoma volume, ml	13.3 (7.5–27.5)	12.3 (7.3–25.7)	0.59
24-hour hematoma volume, ml	13.9 (7.8–34.0)	13.7 (8.0–40.2)	0.36
Baseline IVH volume	2.5 (0.2–9.6)	3.2 (0.0–12.6)	0.32
24-hour IVH volume	4.3 (1.5–12.5)	6.4 (1.6–15.3)	0.15
Baseline deep location of hematoma	186 (82%)	199 (87%)	0.09
Baseline intraventricular hematoma extension	178 (78%)	171 (75%)	0.44

Data are n (%), mean ± SD, or median (IQR).

¹ Scores on the Glasgow Coma Scale range from 15 (fully conscious) to 3 (deep coma). ² Scores on the NIHSS range from 0 (normal neurologic status) to 42 (coma with quadriplegia).

No significant differences were observed in absolute or adjusted mean IVH growth between intensive and guideline BP-lowering treatment [3.4 (95% confidence interval 1.2–5.5) vs. 4.8 ml (2.7–6.9), $p = 0.35$; 1.6 (0.2–3.1) vs. 2.2 (0.8–3.7), $p = 0.56$, respectively]. Patients with an achieved systolic BP over 24 h ≥ 160 mm Hg were younger, more likely to be from China, and had a higher baseline BP (online suppl. table 1). There was a nonsignificant trend towards a greater absolute and adjusted mean IVH growth of 3.58 ml (1.56–5.72) and 3.94 ml (1.46–6.61), respectively, with a mean achieved systolic BP over 24 h ≥ 160 mm Hg (fig. 1). Patients with IVH growth were older, had higher National Institutes of Health Stroke Scale (NIHSS) scores, larger 24-hour ICH volumes, and smaller baseline IVH volumes (online suppl. table 2). The odds ratio for death or major disability was significantly greater with than without IVH growth (adjusted odds ratio 3.51, 95% confidence interval 2.05–6.02; online suppl. table 3).

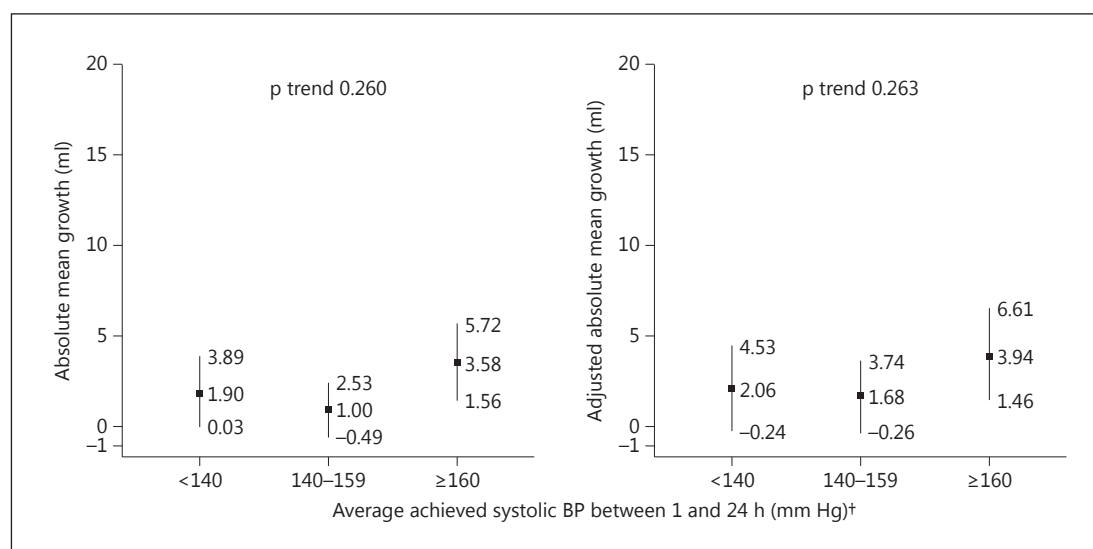


Fig. 1. Intraventricular volume growth by average achieved BP between 1 and 24 h after randomization. [†] Assessed by ANCOVA adjusting for age, sex, China region, use of statin, baseline systolic BP, randomized treatment, baseline IVH volume, and ICH location. Because of skewed raw data, adjusted means are reported with 95% confidence intervals obtained by back-transformation.

Discussion

This post hoc analysis of 456 IVH patients from the INTERACT CT substudies showed no clear relationship between IVH growth in acute ICH and a strategy of early intensive BP management, supporting an earlier analysis of the INTERACT2 study of no association of BP and IVH volume [1]. Thus, the clinical benefits of intensive BP lowering on functional outcome seen in the INTERACT studies are likely attributable to mechanisms other than IVH expansion.

These results concur with a previous small prospective cohort study, where again no significant difference in admission systolic BP or mean BP across categories of IVH volumes within the first 24 h of ICH onset was reported [5]. However, the mean 24-hour IVH volume was still higher in our standard BP treatment group, though not significantly different from intensive BP lowering. BP should not be excluded as a contributing factor to IVH growth. Whilst baseline BP per se does not appear to be a major factor in the pathogenesis of IVH, there was a trend towards a greater IVH volume growth at higher average achieved systolic BP over the first 24 h. Indeed, further analyses of the INTERACT2 study showed that rapid and sustained systolic BP reduction was associated with less ICH hematoma growth over 24 h [6]. Another consideration relates to whether intensive BP reduction is associated with a lower risk of developing IVH. We previously reported that delayed IVH is associated with a worse prognosis, though neither intensive BP lowering nor deep location of ICH were significantly associated with delayed IVH [7].

Whilst the strengths to this study include having a robust, well-characterized cohort from large international trials with standardized care, there are several limitations that include the exclusion of patients with large ICH volumes and impaired Glasgow Coma Scale, which makes the results less generalizable to more severe ICH. Furthermore, despite the large sample size, it is still too small to provide precise estimates of a modest effect of early intensive BP lowering on IVH.

In summary, early intensive BP lowering according to the INTERACT protocol had no clear effect on IVH growth, although the lowest IVH growth was achieved in patients with sustained BP control over 24 h.

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